REMARKS

The Office Action

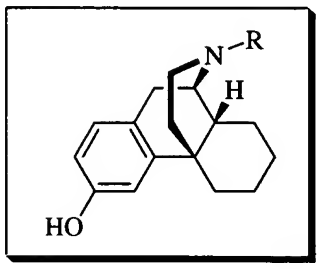
Claims 1-22 are pending in this application. Claims 2, 3, 5-7, 9, 10, 12-15, and 17-22 are withdrawn from consideration. Claims 1, 4, 8, 11, and 16 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

Rejections Under 35 U.S.C. § 112, first paragraph

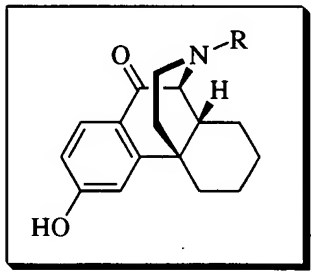
Claims 1, 4, 8, 11, and 16 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner asserts that the specification "while being enabled for R as given in claim 10 does not reasonably provide enablement for any and all heterocyclyl, aryl, alkylaryl, alkylheterocyclyl, and heteroalkyl." As noted by the examiner, the standard for enablement is articulated in *In re Wands* 858 F 2d. 731, 8 USPQ2d 140, 1402 (Fed. Cir. 1988). *Wands* sets forth eight factors to be taken into account to determine whether the experimentation necessary to practice the scope of the claimed invention is "undue." In presenting each of the factors, the examiner concedes that the level of skill in the art is high and the predictability in the art is high. The examiner's rejection appears to be based upon the (i) the amount of guidance provided in the specification; (ii) the working examples; and (iii) the quantity of experimentation necessary, concluding that "it is not seen where the instant specification enables the ordinary artisan to make and/or use the instantly claimed invention." Applicants

respectfully disagree.

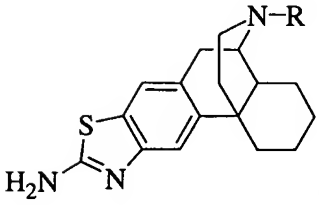
Amount of Guidance Provided in the Specification: The specification provides ample guidance for claims of the present scope. For example, the specification, at pages 10-16, provides definitions for the terms alkyl, alkenyl, alkynyl, heterocyclyl, aryl, alkaryl, alkheterocyclyl, and heteroalkyl. Applicants note that in the broadest claim, claim 1, R is selected from H, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, and C_{1-7} heteroalkyl. Pages 10-16 of the specification provides numerous examples of each class of substituent. Example 1, at pages 21-22, provides a description of how to make morphinan and 10-keto-morphinan intermediates. These are converted to compounds of formulas II, III, and IX as described in examples 4 and 6, respectively.



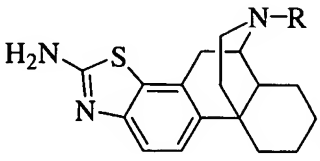
morphinan derivatives



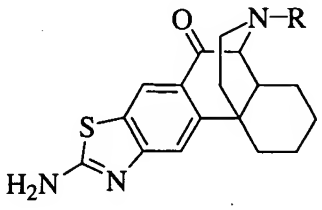
10-keto-morphinan derivatives



(II)



(III)



(IX)

The synthesis begins with a commercially available compound, levorphanol, which is subsequently demethylated (see page 22, Scheme 1, step b), followed by substitution of the resulting secondary amine nitrogen with R (see page 22, Scheme 1; two methods are provided: (i) reaction with RX as shown in step d and (ii) reaction with RCOCl followed by reduction with $LiAlH_4$ as shown in steps e and f). The addition of R, whether C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl, is a synthetically trivial matter, which was well known in the art at the time of filing. See Neumeyer et al., *Bioorganic & Medicinal Chemistry Letters* 11:2735 (2001) and Neumeyer et al., *Journal of Medicinal Chemistry* 43:114 (2000), Exhibits A and B respectively, each of which is submitted herewith. These references show that morphinan derivatives bearing a variety of R groups were known in the art. Subsequent conversion of the morphinan derivative to a compound of the invention is achieved using the methods described in the examples. The specification, at pages 34-37 (examples 12-15) describes how the compounds of the invention can be assayed. Finally, the specification, at pages 18-21, describes how the compounds of the invention can be formulated and administered.

Working Examples: Applicants provide a fully enabling disclosure of how to practice the claimed invention, including several working examples (see page 40, compounds **69**, **70**, **71**, and **72**. Applicants point out that the Federal Circuit has made clear the level of teaching needed to enable a claim with respect to the number of working

examples, and has stated that a specification need not contain even one working example if the invention is otherwise disclosed in such a manner that one skilled in the art is able to practice it without undue experimentation. See *In re Walter L. Borkowski and John J. Van Venrooy*, 422 F2d 904, 164 UPSQ 642 (Fed. Cir. 1970) (eleven step method for preparing an oxygenated hydrocarbon, found to be enabled by the specification absent a working example). See also *In re Roger A. Long*, 368 F.2d 892, 151 USPQ 640 (Fed. Cir. 1966). ("The absence of a working example, denominated as such, does not compel the conclusion that a specification does not satisfy the requirement of 35 USC § 112...").

Quantity of Experimentation Necessary: The Examiner concludes that because there are few working examples in the specification, one of ordinary skill in the art would be required to engage in undue experimentation in order to make and use the claimed combinations. Applicants disagree.

Applicants submit that the Examiner has reinterpreted the *Wands* factors to render them more stringent than the statute or case law, including *Wands*, permits. Under the standard of enablement, an Applicant is required to provide sufficient information to allow practice of the invention, not to provide a detailed synthesis for all possible embodiments.

In re Wands involved a method for identifying monoclonal antibodies that are specific for a particular antigen. The method required screening large numbers of hybridomas to determine which ones secrete an antibody with the desired characteristics.

It was accepted that identification of useful hybridoma lines required substantial experimentation, and was a rare event. The broad claim was held enabled nonetheless. Similarly, the use of the present invention may require testing, based on a variety of predefined parameters (e.g., toxicity and efficacy), in order to optimize new therapeutic regimens including the compounds of the invention. This does not mean the claims are not enabled.

The specification teaches how the compounds of the invention can be synthesized, how they can be administered, and for what therapeutic purposes. The specification provides ample guidance to allow the skilled artisan to make and use the claimed compositions with routine experimentation. As was stated in *In re Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is known in the art. MPEP 2164.01. As noted above, the prior art provides significant teaching regarding the placement of substituent R in the precursors to the compounds of the invention (see Exhibits A and B). Applicants submit that, given the teaching of the specification and the level of skill known in the art at the time the present

application was filed, as detailed above, one skilled in the art could make and use the compounds of the present invention, without undue experimentation, and of the full scope of the claims.

In view of the arguments above, applicants request that the rejection for lack of enablement be withdrawn.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the Office action for three months, to and including Monday November 14, 2005, as Friday November 11, 2005, fell on a holiday, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: November 14, 2005

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